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REMARKS

The Office action of September 15, 2005, has been carefully considered.

A number of objections have been raised to the specification. In view of the extensive changes required, a substitute specification has been submitted. In this substitute specification, 1) subject matter headings have been added, 2) Examples and Tables have been renumbered so that the numbering is consecutive, and 3) sections of the specification have been rearranged in logical sequence. No new matter has been added.

Claims 1-10 and 33 have been rejected under 35 USC 112, 2nd paragraph, on the basis that essential steps have been omitted.

Claims 1 and 13 have been amended to recite a period of administration of 21 to 25 days, as suggested in the Office Action, and claims 12 and 33 have been canceled. Withdrawal of the rejection is requested.

New claim 34 recites continuous administration, as supported in the specification as filed at page 4, lines 4-5.

It is further noted that claims 1, 13 and 34 recite a dosage of 0.5 mg to 3 mg of estradiol and 1.5 mg to 3.75 mg of nomegestrol acetate, which is supported by the specification of Application Serial No. 09/284,147, and it is submitted that all claims are entitled therefore to a filing date of October 8, 1997, the filing date of PCT/FR97/01792.

Claims 1-10, 12-27 and 29-33 as filed in response to the previous action were rejected under 35 USC 103(a) as being unpatentable over Jamin in view of Power et al, Bazin et al, Paris et al and Hodgen.

The Office Action states that "*Jamin discloses a combination of 5 mg per day of nomegestrol acetate and*

transdermal estradiol at 50 µg per day".

Jamin describes a contraceptive method using a high dose of progestin alone to be administered to women who had contra-indications to standard estro-progestin oral contraception, namely, hypertension, thrombotic risks, hyperlipidemia, diabetes and in particular in smokers. The contraceptive method described by Jamin, requires an oral dose of nomegestrol acetate of 5 mg. A major drawback accompanying the method of Jamin was hypoestrogeny and consequently, a poor bleeding pattern, as a result of which Jamin added a low dose of 50 µg of estradiol transdermally. This added estradiol did not contribute to the contraceptive effect; its sole role was compensation of the hypoestrogeny induced by the high dose of nomegestrol acetate. In fact, the estradiol could not have had any contraceptive effect, due to its low dose.

In contrast thereto, the application claims a method of achieving contraception in a woman comprising daily administering to the woman, for a period of 21 days to 25 days, a pharmaceutical composition comprising:

0.5 to 3 mg estradiol, an ester thereof or an equine conjugated estrogen; and

1.5 to 3.75 of nomegestrol acetate.

The invention is directed to the unexpected and never before described potentiation of the antiovulatory activity of nomegestrol by estradiol or its derivatives resulting in the subject contraceptive method using low doses of the progestogen nomegestrol acetate.

In order to better show this unexpected potentiation, submitted herewith is declaration signed by inventor Jean-Louis THOMAS presenting the results of testing carried out according to the protocol of Example IV of the amended specification.

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Figures 1 and 2 of this declaration are a plot of the data obtained in this study, clearly showing that in the presence of estradiol, LH and FSH levels are statistically lower than levels observed when nomegestrol acetate is administered alone.

Another major difference between the invention and the Jamin disclosure is that Jamin's ratio of estrogen to progestogen is completely different from Applicant's ratio. Thus, in Jamin, there is 100 times more progestogen than estrogen (5 mg nomegestrol acetate: 0.05 mg estradiol). In the claimed invention, there is at most 7.5 times as much progestogen as estrogen (3.75 mg nomegestrol acetate: 0.5 mg estradiol).

Therefore, there are many differences between the present invention and Jamin:

1. Jamin does not disclose or suggest a dosage of 1.5-3.75 nomegestrol acetate for use in his contraceptive method;

2. Jamin does not disclose or suggest combining this low dose of nomegestrol acetate with 0.5 to 3 mg estradiol. Jamin adds only 0.05 mg of estradiol to his 5 mg of nomegestrol acetate, i.e. only one tenth the amount estradiol in comparison to the lowest dose of estradiol claimed (i.e. 0.5 mg) according to the invention. Jamin added this low dose of estradiol in order to compensate the hypoestrogeny induced by the high dose of nomegestrol acetate. The estradiol in Jamin had no, and could not have had, due to its low dose, any contraceptive effect. On the other hand, the higher dose of estradiol added to the nomegestrol acetate in the present invention potentiated the contraceptive effect of nomegestrol acetate thereby enabling the use of a lower dose of nomegestrol acetate while still maintaining the contraceptive effect.

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3. In Jamin, the low dose of estradiol is administered transdermally. There is no motivation or incentive in Jamin to change the form of administration from transdermal administration to oral administration.

4. In Jamin, the high dosage of nomegestrol acetate and the low dose of transdermal estradiol is administered for cycles of 20-28 days. There is no motivation or incentive in Jamin to administer the contraceptive specifically for 21-25 days.

Thus, there is no motivation or incentive in Jamin to lower the dose of nomegestrol acetate, lower the dose of nomegestrol acetate and add a higher dose of estradiol, and certainly not to lower the dose of nomegestrol acetate and add a higher dose of estradiol and administer this estradiol orally, and most certainly not to lower the dose of nomegestrol acetate and add a higher dose of estradiol and administer this estradiol orally and administer this combination for 21-25 days.

These many deficiencies are not overcome by any one of the other cited references, alone or in combination.

Powers et al discloses the pharmacokinetics and pharmacodynamics of transdermal dosage forms of 17 β-estradiol and compares them with conventional oral estrogens used for hormone replacement. Thus, the study of Power et al. concerns menopausal women, who have a physiology totally different from that of women of child bearing age; in particular the LH and FSH levels are higher in post menopausal women than in women of child bearing age.

The Office Action states that: "Powers et al. disclose that transdermal estradiol at 0.025, 0.05 or 0.1 mg/day is comparable to oral dosages of estradiol of 2 mg and 1.25 mg of conjugated equine estrogens".

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Applicants disagree with this interpretation of Powers et al. In fact, the conclusion of Powers et al is just the opposite. Powers et al, in the abstract, recites: *"The transdermal systems delivered either 0.025, 0.05, or 0.1 mg/day; oral dosages were 2 mg of micronized 17β-estradiol or 1.25 mg of conjugated equine estrogens".*

Powers et al then continue to state that: *"Serum levels of estradiol obtained 24 hours after oral administration of estrogens were in a range similar to the steady-state levels obtained with transdermal estradiol delivery. Oral estrogens, however, induced an excessive rise in estrone to levels far beyond those observed in premenopausal women".* (underlining added).

Moreover, on page 1105, right column, Powers et al state that *"The oral route of administration for estrogens is, obviously, inefficient and gives rise to a nonphysiologic pattern of metabolites".* (Underlining added)

In other words, if anything, Powers et al teaches away from the invention since Powers et al teach away from a change from transdermal administration of estradiol to oral administration.

Bazin et al discloses that doses of 1.25, 2.5 and 5 mg per day of nomegestrol acetate inhibit ovulation. However, Bazin et al also state that *"Treatment with NOM Ac, 1.25 mg/day, blocks ovulation, but oestradiol concentrations are increased as a result of unimpaired follicular maturation."* (see page 1202, left column last paragraph).

In other words, according to Bazin et al, this dosage of nomegestrol acetate cause an undesired increase in endogenous estrogen levels. Thus, Bazin et al teach away from the present invention since in the present invention Applicants are adding 0.5-3 mg estradiol and not reducing estradiol.

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Paris et al indeed disclose the lack of side-effects of nomegestrol acetate. However, Paris et al do not remedy any one of the deficiencies mentioned above with respect to Jamin. Moreover, this study was performed in animals (rodents) and not in women.

Paris et al do not mention or discuss possible dosages of nomegestrol acetate for use in contraception, nor do they discuss combining nomegestrol acetate with estradiol. Paris et al certainly do not disclose the potentiating contraceptive effect of the higher dose of estradiol added to the nomegestrol acetate in the invention thereby enabling the use of a lower dose of nomegestrol acetate while still maintaining the contraceptive effect.

Furthermore, there is no discussion on dosages of estradiol to be used. Most certainly there is also no discussion on which form of administration should be used nor the regimen to be used. Paris et al in fact, do not even teach a method of contraception, but merely question whether this compound may be useful in contraception (last line of the article), but do not conclude that this is so. Even assuming, *arguendo*, that Paris et al concluded that this compound would be useful in contraception, there is no disclosure in Paris et al about any one of the elements of the subject invention nor is there any indication of such elements.

Hodgen describes a method of female contraception. Hodgen however does not even mention the progestogen nomegestrol acetate and therefore cannot possibly remedy the deficiencies of Jamin et al. Moreover, there is no motivation or incentive in Hodgen to replace the progestogens mentioned therein with nomegestrol acetate.

In conclusion, none of the cited references, alone or in combination, teaches or suggests the invention as claimed, and

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withdrawal of the rejection is requested.

Claims 1-10, 12, and 17-33 have been rejected under 35 USC 103(a) as being unpatentable over FR 2754179 in view of Hodgen. The French publication is a publication of the present priority application. As all claims in the application are entitled to the original filing date of October 8, 1997 (the filing date of PCT/FR97/01792), and the French publication was published subsequent to this date, Applicants submit that the French publication is not prior art to the present application, and this rejection should be withdrawn.

In view of the foregoing amendments and remarks, Applicants submit that the present application is now in condition for allowance. An early allowance of the application with amended claims is earnestly solicited.

Respectfully submitted,

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